UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,797	02/11/2004	Gregory Grabowski		4885

7590 11/21/2007

FROST BROWN TODD LLC
2200 PNC Center
201 E. Fifth Street
Cincinnati, OH 45202-4182

EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
11/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/776,797	GRABOWSKI ET AL.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-65* is/are pending in the application.

4a) Of the above claim(s) *37-50 and 62-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 June 2004 and 11 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 09/12/2007 has been entered. A complete list of claim is present and each claim has been provided with the proper claim identifier. Claims 1-36 and 66-68 were cancelled. Claims 37-65 are pending. Claims 51, 54, 56 are amended. Claims 51-61 are currently under examination.

Claims 37-50 and 62-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

This application 10/776,797 filed on 02/11/2004 is a DIV of 09/775,517 02/02/2001 PAT 6,849,257 which claims benefit of 60/180,362 02/04/2000.

Specification

1. Applicant's amendment to the specification is noted. The priority information has been updated to reflect the current status of the priority documents in the reply filed on 08/07/2007. Applicant updated the status of parent application 09/775,517, filed on February 2, 2001 as US Patent No. 6,849,257.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. The rejection of claim 54 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because the inclusion of claim 54 in the rejection set forth at page 4 of the office action dated 03/07/2007 appears to be the result of an typographic error.

Claim 55 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It was previously noted that there is no polypeptide sequence of any lysosomal acid lipase disclosed in the specification. The phrase "substitution of amino acid Pro (-6) to Thr and Gly2 to Arg" recited in claim 55 of instant application is vague and indefinite. Does Gly2 indicate the second amino acid of the recited lysosomal acid lipase being an amino acid residue glycine? It is also unclear what "(-6)" means in the term "Pro(-6)".

Applicant's arguments: Applicant argues that, with respect to the lysosomal acid lipase sequence, both the amino acid and DNA sequence were published and well known in the art at the time of filing. In particular, Ameis et al., *Eur. J. Biochem.* 1994, reference cited by applicants at paragraph [0037] discloses the cDNA and peptide sequence sufficient to enable the instant invention. With respect to claim 55, the nomenclature used would readily be understood to one of skill in the art at the time of filing. To clarify, Applicant states that, "Gly2 to Arg" indicates that the naturally occurring amino acid at position 2 in lysosomal acid lipase is mutated from glycine to arginine. *Likewise, "Pro (-6) to Thr" indicates the proline residue six amino acids upstream of the first amino acid of the lysosomal acid lipase protein is mutated to a*

threonine. As such, applicants' assert that the claim is not vague or indefinite, and the rejection to the claim should be withdrawn.

Response to Applicant's arguments: Applicant's arguments filed 09/12/2007 have been fully considered and they are not persuasive. The Examiner has carefully reviewed the cited reference by Ameis et al. (Ameis et al., Purification, characterization and molecular cloning of human hepatic lysosomal acid lipase. *Eur J Biochem.* 219(3): 905-14, 1994). Ameis et al. disclosed that the second amino acid residues of the deduced protein sequence for human lysosomal acid lipase (LAL) cDNA is Lysine, not a glycine (See Figure 6, page 911, Ameis et al., 1994). It remain unclear what is encompassed by "Gly2 to Arg" recited in claim 55. Moreover, Applicant's statement, "Pro (-6) to Thr" indicates the proline residue six amino acids upstream of the first amino acid of the lysosomal acid lipase protein is mutated to a threonine, appears to be an oxymoron made up of contradictory or incongruous elements. It is totally perplexing regarding what "six amino acids upstream of the first amino acid of the lysosomal acid lipase" really is. The Examiner notes that the 5' un-translated region (5 UTR) at nucleotide level is usually marked by minus numbers (See Figure 6, page 911, Ameis et al., 1994), but there is no amino acid residue before the first initiation methionine (Met) residue of a given protein.

3. Claims 51-55 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendments filed by Applicant on 09/12/2007.*

The amended claim 51 recites the limitation "the sequence" in the phrase "wherein the sequence contains the catalytic lipase triad Asp-Ser-His". There is insufficient antecedent basis for this limitation in the claim. The sequence appears to refer to a given polypeptide sequence, however, the claim only recites a DNA sequence in line 4 of claim 51. Furthermore, the phrase "catalytic lipase triad Asp-Ser-His" is unclear in terms of the order of these three amino acid residues with respect to N-terminus and C-terminus of the lipase polypeptide, and whether these three amino acid residues are in consecutive order or not. Claims 52-55 depend from claims 51.

Claim 54 is unclear with respect to the newly added limitation "showing biological activity *similar to* that of lysosomal acid lipase". The specification does not define what biological activity is considered as "biological activity similar to that of lysosomal acid lipase". Accordingly, the metes and bounds of the phrase "biological activity *similar to* that of lysosomal acid lipase" are unclear. As an example, a broad and reasonable interpretation of the phrase would encompass a given mutated form of the lysosomal acid lipase retains only 1% of biological activity of a non-mutated lysosomal acid lipase, as measured by kinetic parameters pertaining to enzymatic activity and/or thermodynamic parameters pertaining to the stability of the enzyme.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 51-61 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant's arguments filed 09/12/2007 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 4-7 of the office action mailed on 03/07/2007.

Applicant's arguments

With regard to the claim rejection directed towards *lipid hydrolyzing protein or polypeptide acid lipases* (claims 51- 55) as lacking sufficient structure that would provide any reliable information about the structure of other lysosomal acid lipase DNAs, Applicant argues that claim 51 has been amended to more clearly define the structural relationship to other lipid hydrolyzing protein cDNA. Specifically, claim 51 now claims lipid hydrolyzing protein sequences which contain the catalytic lipase triad Asp-Ser-His. Applicant indicates that this amendment to the claims demonstrates a specific structural relationship to other lipid hydrolyzing proteins. Applicant also indicates that the Ser of the catalytic lipase triad Asp-Ser-His is Ser^{153} (which Examiner notes Ser^{153} is not recited in the amended claim 51). As such, Applicant argues that one of ordinary skill in the art would recognize other proteins or polypeptides (i.e., those containing the catalytic lipase triad of amino acids), which could be used with the instant invention.

With regard to the claim rejection directed towards *lysosomal acid lipases* (claims 56-61) as lacking sufficient structure that would provide any reliable information about the structure of other lysosomal acid lipase DNAs, Applicant argues that the lysosomal acid lipase protein was

well characterized at the time the instant application was filed. In particular, Applicant argues that, as noted by applicants at paragraph [0037], conserved regions of lysosomal acid lipase were known and published prior to filing of the instant application. Applicant argues that, in general, the level of skill in the art is such that knowledge of conserved regions in a protein allows one to predict the general structure of operable variants such that every variant need not be disclosed. Further, at the time of filing, a functional assay was available which could be used to identify active lipid hydrolyzing proteins, particularly LAL. See Sheriff, et al., *J. Biol. Chem.* 1995; 270:27766-27772, a copy of which is enclosed. As such, Applicants argues that applicants were, in fact, in possession of the genus of lysosomal acid lipase DNAs, and that one of skill in the art could readily ascertain biologically active LAL or lipid hydrolyzing proteins or polypeptides.

With regard to the rejection of claim 54 in view of the phrase "at least 85% homology", Applicant argues that claim 54 has been amended to clarify the claim and claim 54 now refers to sequences or polypeptides having at least 85% sequence homology to lysosomal acid lipase *showing biological activity similar to that of lysosomal acid lipase.*

Response to Applicant's arguments

It is noted that the specification of instant application does not disclose any specific DNA sequences that encode any specific *lipid hydrolyzing protein or polypeptide*, not even a species of DNA sequences that encode any lysosomal acid lipase encompassed by the enormous genus claimed as hydrolyzing protein or polypeptide. In the absence of these directly relevant information, Ser^{153} residue (which Examiner notes Ser^{153} is not recited in the amended claim 51) cannot even be identified because the number of a given amino acid residue needs a reference in

the context of a given polypeptide. As an example, the reference 31 cited by Applicant in paragraph [0037] published by **Ameis et al.,** 1994 disclosed the human lysosomal acid lipase (LAL) cDNA and protein sequence, which is 372 amino acid protein (See Figure 6, Ameis et al., Purification, characterization and molecular cloning of human hepatic lysosomal acid lipase. *Eur J Biochem.* 219(3): 905-14, 1994). In this regard, the data presented by Ameis et al., 1994 are consistent with the disclosure in paragraph [0037] of instant application, indicating LAL is a 372 amino acid glycoprotein (See first sentence of paragraph [0037], US 2004/0223960, publication of instant application). However, amino acid residue at position 153 disclosed by Ameis et al., 1994 is Glycine, not Serine. In this regard it is noted that the newly added limitation "wherein the sequence contains the catalytic lipase triad Asp-Ser-His" does not recite the Ser as Ser 153. Regardless, the metes and bounds of the limitation is unclear as discussed in the preceding section of the rejection of claims 51-55 under 35 U.S.C. 112, second paragraph. Furthermore, the post-filing art by **Koffel et al.** identified that yeast lipases bearing amino acid residues of the catalytic triad of lipases are encoded by YLL012/YEH1, YLR020/YEH2, and TGL1, and are paralogues of the mammalian acid lipase family, *which is composed of the lysosomal acid lipase, the gastric lipase, and four novel as yet uncharacterized human open reading frames* (See abstract, and Figure 4, Koffel et al., The *Saccharomyces cerevisiae* YLL012/YEH1, YLR020/YEH2, and TGL1 genes encode a novel family of membrane-anchored lipases that are required for steryl ester hydrolysis. *Mol Cell Biol.* 25(5): 1655-68, 2005).

With regard to the claim rejection directed towards *lysosomal acid lipases* (LAL, claims 56- 61), Applicant's arguments that, in general, the level of skill in the art is such that knowledge of conserved regions in a protein allows one to predict the general structure of operable variants

such that every variant need not be disclosed are found not persuasive. In this regard, the post-filing art by **Zschenker et al.** identified and characterized K49R and G50A mutant LAL. The mutant K49R showed wild-type LAL activity, but mutant G50A showed significantly reduced enzyme activity compared to wild-type LAL and a greater reduction in culture medium than in detergent cell extracts. Kinetic data suggest that mutant G50A is less stable than wild-type LAL and mutant K49R; in contrast to K49, the highly conserved amino acid residue G50 seems to be in a very important position and its mutation influences both secretion and enzyme activity of LAL (Zschenker et al., Lysosomal acid lipase as a preproprotein, *J Biochem (Tokyo)*, 136(1): 65-72, 2004). It is worth noting, as discussed on pages 5-6 of the Non-Final office action dated 03/07/2007, that the specification does not disclose any nucleotide sequence that encodes a lysosomal acid lipase from mammalian lipase DNAs or human lipase DNAs or other lysosomal acid lipase DNAs from other cell types. There is no evidence on the record of a relationship between the structure of any lysosomal acid lipase cDNA and the claimed lysosomal acid lipase DNA that would provide any reliable information about the structure of other lysosomal acid lipase DNAs within the genus. There is no evidence on the record that the asserted lysosomal acid lipase DNA had a known structural relationship to any other lysosomal acid lipase cDNA sequences; the specification discloses none of lysosomal acid lipase DNA obtained from any origin; the art indicated that there is variation between lysosomal acid lipase DNA sequences and their functions.

With regard to the rejection of claim 54 regarding the amended limitation "at least 85% sequence homology to lysosomal acid lipase showing biological activity similar to that of lysosomal acid lipase", it is noted that the recited "85% sequence homology" reads on any

portion of any given protein that shows biological activity similar to that of lysosomal acid lipase. Moreover, as discussed on page 7 of the Non-Final office action dated 03/07/2007, based on the information disclosed in the specification of instant application, a lysosomal acid lipase (LAL), a member of the lipase family, is a 372 amino acid glycoprotein (See lines 1-2, paragraph [0037], instant application). Accordingly, 15% of 372 amino acids would account for more than 55 amino acids. Each amino acid could be altered to one of the other 19 amino acid residues (when only L-form standard amino acid residues is considered); thus, there would be 19^{55} different variations, which is equivalent to 2.1×10^{70} different patentably distinct polypeptides. Relevant to the issue of recited "85% sequence homology", the post-filing art by **Soyombo et al.** identified mutations in the ion channel mucolipin 1 (TRP-ML1) and characterized that TRP-ML1 can function as a H (+) channel, and the increased lysosomal acidification. The measurement of lipase activity using several substrates revealed a marked reduction in lipid hydrolysis in TRP-ML1 (-/-) cells, which was rescued by the expression of TRP-ML1 (See abstract and Figures 1 and 4, Soyombo et al. TRP-ML1 regulates lysosomal pH and acidic lysosomal lipid hydrolytic activity, *J Biol Chem.* 281(11): 7294-301, 2006).

In conclusion, the specification was not described in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, Applicant had possession of the claimed invention recited in claims 51-61.

5. Claims 51-61 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with

which it is most nearly connected, to make and/or use the invention. Applicant's arguments filed 09/12/2007 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 7-13 of the office action mailed on 03/07/2007.

Applicant's arguments

With regard to the citation of Wolf et al. 2005 on pages 5-6 of the Non-Final office action, Applicant stated that it's not clear why the reference was cited.

Applicant argues that the references offered by the Office actually support a finding that gene therapy techniques are within the skill of the art at the time of filing, such that undue experimentation is not required. In Read, et al., at p. 21, for example, the authors note that administration of DNA/lipid mixtures is safe and can produce clinically significant responses. Further, hydrodynamic delivery to the liver via a superficial vein is referred to as the simplest successful in vivo delivery route, having few barriers to delivery. (Read, et al., p.22).

Applicant further argues that at the time of filing the level of skill in the art is high, and Applicant provides the following references regarding successful administration of genes to produce biologically active proteins:

- Rosengart, T, "Angiogenesis Gene Therapy: Phase I Assessment of Direct Intramyocardial Administration of an Adenovirus Vector Expressing VEGF 121 cDNA to Individuals with Clinically Significant Severe Coronary Artery Disease," Circulation 1999; 100:468-474, "Rosengart I"; and Rosengart, T., et al., "Six-Month Assessment of a Phase I Trial of Angiogenic Gene Therapy for the Treatment of Coronary Artery Disease Using Direct Intramyocardial Administration of an Adenovirus Vector Expressing the VEGF 121 cDNA," Annals of Surgery 1999; 230: 455-472, "Rosengart II."

- Losordo, D.W., et al, "Gene Therapy for Myocardial Angiogenesis: Initial Clinical Results with Direct Myocardial Injection of phVEGF 165 as Sole Therapy for Myocardial Ischemia," Circulation 1998; 98:2800-2804.
- Shetty, K. et al, "Gene therapy of hepatic diseases: prospects for the new millennium," Gut 2000; 46:136-139
- Hirschowitz, E., "Regional treatment of hepatic micrometastasis by adenovirus vector-mediated delivery of interleukin-1 and interleukin-12 cDNAs to the hepatic parenchyma," Cancer Gene Therapy 1999; 6:491-498.

Applicant argues that in Rosengart I and II, both published in 1999, a recombinant adenovirus (Ad) gene transfer vector containing vascular endothelial growth factor (VEGF) cDNA was successfully administered directly to an ischemic area of the myocardium in patients with coronary artery disease, showing cardiovascular improvement both one and six months after treatment with the gene. Applicant also argues that Losordo et al. demonstrates successful gene transfer of DNA (encoding VEGF) to the myocardium, and Losordo showed no operative complications, and marked symptomatic improvement and/or objective evidence of improved myocardial perfusion in all patients. Applicant further argues that Shetty et al. described successful methods of gene delivery to the liver, including retroviral vectors, adenoviral vectors, adeno-associated vectors, simian virus 40 vectors, and hybrid viruses. As a final example, Applicant argues that Hirschowitz et al. demonstrate successful use of adenovirus vector-mediated delivery of DNA sequences to produce high levels of corresponding protein in the liver.

With regard to additional non-enabled aspect of claim 54 pertaining to the limitation "at least 85% sequence homology to lysosomal acid lipase", Applicant argues that claim 54 has been amended to recite "at least 85% sequence homology to lysosomal acid lipase showing biological

activity similar to that of lysosomal acid lipase", thereby the practice of the invention with respect to this claim would merely require routine experimentation.

Response to Applicant's arguments

With regard to the citation of Wolf et al. 2005 on pages 8-9 of the Non-Final office action dated 03/07/2007, the Examiner clarifies that the citation of Wolf et al. was intended to set the stage for the discussions of the key element of the claimed gene therapy subject matter, i.e. the roles of lipid hydrolytic proteins, in particular lysosomal acid lipase, in lipid metabolism.

With regard to the references pertaining to unpredictability of gene therapy cited by Examiner (Pouton et al., 2001; Johnson-Saliba et al., 2001, Read et al., 2005, Dobson et al., 2006), Applicant argues that in Read, et al., at p. 21, the authors indicates that administration of DNA/lipid mixtures is safe and can produce clinically significant responses. Applicant further argues that in Read, et al., p.22, the authors indicate that hydrodynamic delivery to the liver via a superficial vein is referred to as the simplest successful in vivo delivery route, having few barriers to delivery. In response, the Examiner notes that the key message of citing Pouton et al., 2001; Johnson-Saliba et al., 2001, Read et al., 2005, and Dobson et al., 2006 is to show that gene therapy is unpredictable and the enabling support of a given claimed gene therapy is evaluated on a case-by-case basis. In other words, the Examiner's interpretation of these cited references is that gene therapy is unpredictable and many factors need to be considered, including the characteristics of the gene and its product, the vector used for delivery, administration of the vector, targeting the gene to desired cells and cellular compartment, initiation and sustained expression of the gene, potential unexpected side effects associated with gene therapy,

extrapolation from animal models to human beings etc. However, it's worth noting that unpredictable is not equivalent to impossible (i.e. no aspect of any gene therapy can be performed successfully). The Examiner's interpretation of these cited references, and the position the Examiner stands on gene therapy in general, is consistent with some positive notes expressed by Read et al., 2005.

With regard to the references cited by Applicant, these references have been fully considered and they are found not persuasive because none of these references provides enabling support for broadly claimed gene therapy by administration into cells a vector comprising and expressing a DNA encoding either biologically active lipid hydrolyzing protein or biologically active lysosomal acid lipase. The relevance of each individual reference is discussed below.

Rosengart et al. (*Circulation*, 100: 468-474, 1999) and Rosengart et al. (*Annals of Surgery*, 230: 466-472, 1999) are focused on intra-myocardial administration of adenoviral vector expressing VEGF121 cDNA for antiogenic gene therapy of coronary artery disease. Rosengart et al., 1999 do not teach gene therapy by administration into cells a vector comprising and expressing a DNA encoding either biologically active lipid hydrolyzing protein or biologically active lysosomal acid lipase, as claimed by instant application.

Losordo et al. (*Circulation*, 98: 2800-2804, 1999) is focused on direct myocardial injection of plasmid expressing 165 amino acid isoform of human VEGF gene for treating myocardial ischemia. Losordo et al., 1999 do not teach gene therapy by administration into cells a vector comprising and expressing a DNA encoding either biologically active lipid hydrolyzing protein or biologically active lysosomal acid lipase, as claimed by instant application.

Shetty et al. (*Gut*, 46:136-139, 2000) is a general reviews on the prospects for gene therapy of hepatic disease. Shetty et al., 2000 do not teach gene therapy by administration into cells a vector comprising and expressing a DNA encoding either biologically active lipid hydrolyzing protein or biologically active lysosomal acid lipase, as claimed by instant application.

Hirschowitz et al. (*Cancer Gene Therapy* 6: 491-498, 1999) is focused on mouse model of adenoviral vector mediated intravenous (i.v.) delivery of interleukin-2 and interleukin-12 cDNA for regional treatment of hepatic micro-metastasis. Hirschowitz et al. 1999 do not teach gene therapy by administration into cells a vector comprising and expressing a DNA encoding either biologically active lipid hydrolyzing protein or biologically active lysosomal acid lipase, as claimed by instant application.

With regard to claim amendments of claim 54 reciting "at least 85% sequence homology to lysosomal acid lipase showing biological activity similar to that of lysosomal acid lipase", the issue of this claim amendment has been discussed in the section of new rejection of claims 51-55 under 35 U.S.C. 112, second paragraph, of this office action. The claim amendment does not render any more enabling support of claim 54.

In summary, it is worth emphasizing again that the evaluation of enabling support is done on the case-by-case basis. It is also worth noting that the deletion of the phrase "having a deficiency in biologically active lipid hydrolyzing protein or polypeptide" from claim 51, and the deletion of the phrase "having a deficiency in biologically active lysosomal acid lipase" from claim 55 do not significantly alter the breadth of the claimed invention because the deleted phrases are only relevant to the intended use of the products (the DNA sequences encoding

biologically active lipid hydrolyzing protein or polypeptide, and the DNA sequences encoding biologically active lysosomal acid lipase) to desired mammals.

In view of the state of the art, the unpredictability in the art (as discussed above), and the lack of specific guidance and no working examples in the specification (as discussed on page 12 of the Non-Final office action dated 03/07/2007), one of skill in the art would have to perform undue experimentation to make and use the claimed invention as recited in claims 51-61.

Priority

6. This application 10/776,797 filed on 02/11/2004 is a DIV of 09/775,517 02/02/2001 PAT 6,849,257 which claims benefit of 60/180,362 filed 02/04/2000. It is noted that the claims of instant application recites administration into cells a vector comprising and expressing a DNA sequence encoding either biologically active lipid hydrolyzing protein or polypeptide (claim 51) or biologically active lysosomal acid lipase (claim 56). *The provisional application 60/180,362 filed on 02/04/2000 disclosed administration of enzyme into cells, a protein therapy; however, the application 60/180,362 did not disclose administration of DNA sequences encoding the said enzyme.* In this regard, the application 09/775,517 filed 02/02/2001 (now U.S. Patent No: 6,849,257) did disclose vectors expressing proteins. Therefore, the priority of instant application can be dated back to 02/02/2001. Further elaboration is provided in the art rejections below.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 51-54, and 56-61 are rejected under 35 U.S.C. 102(e) as being anticipated by Xiao (Xiao, U.S. Patent Application Publication No: 2004/0038365, Publication date Feb. 26, 2004), is ***withdrawn*** because Xiao cannot be used as an 102 (e) prior art and moreover Applicant filed Declaration under 37 C.F.R 1.131 on 08/07/2007 asserting the conception and reduction to practice of the claimed invention dated prior to January 25, 2001.

It is noted that the PCT/EP01/12382 of Xiao, 2004 was filed 0n 10/26/2001. Since the PCT/EP01/12382 was filed after Nov. 29, 2000 and did not designate US, there is no 102(e) date and Xiao et al. is prior art as of its publication date, i.e. 02/26/2004. However, Applicant's arguments that the priority date of instant application should be the filing date of provisional application 60/180,362 filed on 02/04/2000 are found not persuasive as discussed in more details below.

Applicant's arguments: With regard to the qualification of Xiao et al. as an 102(e) art over the claimed priority date of instant application, Applicant argues that the provisional application 60/180,362 states that the endogenous protein is "produced or manufactured inside the body by some type of device (biologic or other) for delivery to within or to other organs of the body." This encompasses delivery of DNA for production of proteins by cells endogenously. As such, the provisional application provides support for the pending claims, and accordingly,

the priority date of the instant application should be the filing date of this provisional, February 4, 2000, which predates both Xiao and Kapeller-Libermann.

Response to Applicant's arguments: To properly evaluate the disclosure of provisional application 60/180,362, the sentences of lines 8-19 on page 3 are recited below, with underlined sentences correspond to the citation indicated by Applicant's arguments.

However, neither approach offers the potential for direct dissolution of existing atherosclerotic plaques. The use of a suitable lipid-hydrolyzing enzyme, such as LAL offers an alternative. The lipid-hydrolyzing enzyme can be either an exogenous enzyme or an endogenous enzyme. Exogenous enzymes are those produced or manufactured outside of the body and administered to the body. Endogenous enzymes are those produced or manufactured inside the body by some type of device (biologic or other) for delivery to within or to other organs in the body. LAL is present in body tissue. Patients who suffer from atherosclerosis have a tendency to have decreased levels of LAL. This suggests that there may be some link between LAL levels and atherosclerosis. Thus, in the future, a possible screening test for atherosclerosis may be to measure the LAL level in a patient's tissue.

The above citation clearly indicates the disclosure is specifically pertaining to administration of lipid hydrolyzing enzyme, such as LAL, for therapeutic purposes. For instant, it is unambiguously stated that, "The use of a suitable lipid hydrolyzing enzyme, such as LAL offers an alternative". There is no indication whatsoever in these sentences that are pertaining to the claimed invention of instant application regarding "administration into cells a vector comprising and expressing a DNA sequence encoding biologically active lipid hydrolyzing protein", as recited in claim 51, or lysosomal acid lipase as recited in claim 56.

Furthermore, Applicant's arguments that the statement "Endogenous enzymes are those produced or manufactured inside the body by some type of device (biologic or other) for delivery

to within or to other organs in the body", reads on delivery of exogenous DNA for production of proteins in the cells, is found not persuasive at all. It is further noted that the term "endogenous enzymes", in its commonly accepted meanings in scientific literature, would read on those enzymes that are produced inside the body by endogenous genes. Thus, the provisional application 60/180,362 on protein therapy fails to support the gene therapy claimed in instant application. Accordingly, the application 09/775,517 filed 02/02/2001 (now U.S. Patent No: 6,849,257) did disclose vectors expressing proteins, and therefore, the priority of instant application can be dated back to 02/02/2001.

8. Claims 51-54 and 56-61 remain rejected under 35 U.S.C. 102(e) as being anticipated by Kapeller-Libermann (Kapeller-Libermann, U.S. Patent Publication No: 2002/0193303, Publication date, Dec 19, 2002), is ***withdrawn*** because Applicant filed Declaration under 37 C.F.R 1.131 on 08/07/2007 asserting the conception and reduction to practice of the claimed invention dated prior to January 25, 2001.

It is noted that Kapeller-Libermann was filed on Jan. 25, 2002, which claim the benefit of the provisional application No. 60/264,167 filed on Jan. 25, 2001. Therefore, the 102(e) date for Kapeller-Libermann is 01/25/2001..

With regard to whether the instant application can claim benefit of its provisional application 60/180,362 filed on 02/04/2000, ***Applicant's arguments*** and Examiner's ***Response to Applicant's Arguments*** are the same as discussed in the preceding section on the rejection of claims 51-54, and 56-61 are rejected under 35 U.S.C. 102(e) as being anticipated by Xiao.

Conclusion

9. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent

examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Wu-Cheng Winston Shen, Ph. D.
Patent Examiner
Art Unit 1632

/Valarie Bertoglio, Ph.D./
Primary Examiner
AU 1632